Twenty years’ experience with post-Chernobyl thyroid cancer

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Chernobyl, the largest ever nuclear accident, caused a huge release of radioactive isotopes, including nearly $2 \times 10^{18}$ Bq of iodine-131. Four years later an increase in thyroid cancer incidence, virtually all papillary carcinomas in children, occurred in the highly exposed areas. The increase has continued, and with increasing latency the tumour molecular and morphological pathology has changed; further changes may occur in the future. Children under the age of 1 at exposure show the highest susceptibility, and carry this risk with them into adult life; 4000 cases have been attributed to the accident, but so far very few have died. The risk falls rapidly with increasing age at exposure; it is doubtful if there is any risk for adults at exposure. Other factors linked to susceptibility to thyroid carcinogenesis after Chernobyl include dose, iodine deficiency, and genetic factors. Other consequences are briefly covered.

Key words: thyroid cancer; radiation; Chernobyl; latency; genotype–phenotype correlation.

It is over a hundred years since radioactivity was discovered, and over 60 years since the energy contained within the atom was recognized and the techniques to access that energy developed. Two events since then have had a major impact on the public attitude to the use of atomic energy: the atomic bombing of Japan, with the devastation of the cities of Hiroshima and Nagasaki, and the catastrophic nuclear accident at Chernobyl. Like any bombing, the atomic bombs led to death and serious injury; unlike any previous events they led to lifelong effects on the health of the exposed population due to radiation. These effects have been studied in detail; they still are being studied, and have provided most of our current information about the effect of radiation on human health.

The type of radiation exposure after Chernobyl was quite different from the exposures after the atomic bombs. In Hiroshima and Nagasaki well over 100,000 people were exposed to external whole-body radiation from gamma rays and neutrons.
Exposure to fallout from the radioactive isotopes released from the explosion was trivial. After Chernobyl, millions of people were exposed to significant levels of radioactivity from fallout, and if low levels of exposure are included that figure rises to hundreds of millions. External whole-body radiation was relevant only to those working in or close to the reactor, particularly during and in the few days after the accident. The radiation from the released radioactive isotopes was largely beta and gamma radiation. While the whole-body radiation from the bombs affected all organs fairly evenly, and the dose was dependent on distance from the hypocentre, the isotopic radiation from Chernobyl affected organs differently depending on the nature of the isotope, and the dose from fallout was influenced by many factors: time, atmospheric, dietary, and environmental. The health consequences of Chernobyl will therefore differ greatly from those of exposure to the atomic bombs, and studies of the lifetime effects of Chernobyl are equally as important as those of exposure in Hiroshima and Nagasaki.

THE ACCIDENT

The accident at Chernobyl happened on April 26th 1986, it was the result of a combination of an ill-judged experiment, poor reactor design, and human error. The reactor overheated, the graphite core caught fire, there was a steam explosion that blew off the reactor lid, scattered fragments of radioactive fuel and burning graphite in the immediate vicinity, and ‘boiled off’ the volatile isotopes present, releasing in total about $10^{19}$ Becquerel into the atmosphere. The main isotopes released were xenon-133, iodine-131, tellurium-132, and neptunium-239, with smaller amounts of caesium-134 and -137, strontium-89 and -90, and a range of others. Iodine-133 and -135 were also released, but the half-lives of these isotopes are extremely short and they are unlikely to be important for health consequences, apart from to those living close to the reactor. Chernobyl is located in the far north of Ukraine, close to the border with Belarus. The radioactive cloud was at first carried to the north, and the heaviest fallout occurred in the south of Belarus, particularly in the district (Oblast) of Gomel.

The immediate aftermath of the accident was marked by secrecy and confusion. There were no general health precautions, no sheltering, and no effective distribution of stable iodide. Evacuation of the nuclear workers’ town of Pripyat started about 36 hours after the explosion, but evacuation from the designated 30-kilometre exclusion zone continued for weeks. For the first few critical days consumption of locally produced milk and other food continued as usual. Severe short-term health effects were seen in those working on the reactor site who had been exposed to high doses of whole-body radiation. About 150 workers suffered from acute radiation syndrome, 28 died within the first 4 months from skin, bone marrow and intestinal effects. The death rate in this group has risen to over 50, including deaths from diseases such as myeloproliferative disorders. In contrast, those exposed to fallout suffered no serious direct radiation effects in the first few years, although there were considerable psychosocial effects. The consequences of evacuation and relocation, the fear of potential health effects from exposure to unknown amounts of radiation, and particularly concern for children and the destruction of a way of life all contributed to this. The International Atomic Energy Authority (IAEA) arranged a study of the consequences. The delegation visited some of the most affected areas, examined those exposed, held meetings with the inhabitants, and issued a reassuring report that 4 years after the accident there appeared to be no significant health consequences.

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THYROID CARCINOMA INCIDENCE

The first indications of a rise in the incidence of childhood thyroid carcinoma were reported to the International Atomic Energy Agency (IAEA) in 1990, but were not followed up. Over the next 2 years increasing numbers of children with thyroid carcinoma were seen in Minsk, the capital of Belarus, and Kiev, the capital of Ukraine. Reports of this increase reaching countries outside those most affected were largely discounted, because while it was known that external radiation would lead to an increase in thyroid carcinoma, the latent period was thought to be 10 years, and isotopes of iodine were thought to be of very low carcinogenicity or even non-carcinogenic. In 1992 a delegation from WHO Europe visited Minsk, and was shown 12 children with thyroid carcinomas, together with histological sections from 25 cases that had been seen in Minsk in about 6 months. Belarus is a country with about 2 million children, and thyroid carcinoma in children is normally a rare disease, with a UK incidence of the order of 1 case per million children per year, although some tumour registries record a rate several-fold higher. The recorded rate in Belarus before Chernobyl was less than 1 per million. These findings clearly indicated a major increase, and the visit led to two letters to Nature, setting out the number seen, the clinical and pathology confirmation, and making the case for wider studies.3,4 Reviewing the Belarus records the first rise probably started in 1989, only 3 years after the accident; thereafter the number of cases of childhood thyroid cancer rose steadily, reaching about 100/million/year in Gomel Oblast by 1995. The incidence correlated with the level of fallout, highest in Gomel Oblast in the south of Belarus, just over the border from Chernobyl, very low in Vitebsk Oblast in the north of Belarus where fallout was negligible. The incidence of childhood thyroid cancer in Northern Ukraine was also increased, but to a lesser degree than in Gomel. Radiation from administered iodine-131 gives a dose to the thyroid that is up to a thousand times higher than the average dose to other tissues, and there is no doubt that the increased incidence of thyroid cancer is largely if not entirely due to ingestion and inhalation of isotopes of iodine, particularly iodine-131. Analysis of the incidence figures showed that the sensitivity to radiation-induced thyroid carcinoma was critically dependent on age at exposure, with the youngest being most at risk. The rate of increase of childhood thyroid cancer slowed after 1994, the incidence reached a peak and then declined as those who were children at the time of the accident passed into adolescence. As the increase in children declined, so the incidence in adolescents increased; by 2002 the increase in adolescents stopped as those exposed in later childhood became adults(Figure 1).5 While there is no doubt that those exposed as children are carrying their increased risk for thyroid carcinogenesis with them as they become adults, it is still uncertain whether those who were adults at the time of exposure have an increased risk. The incidence of recorded thyroid cancer in adults in the exposed areas has increased since 1990. At least some of this increase is likely to be a result of increased ascertainment, and thyroid carcinoma rates have been increasing globally. Studies of thyroid carcinogenesis after external radiation found no evidence of an increase in adults over 406, but the numbers studied were small compared to the size of the exposed population after Chernobyl. For these, and for theoretical reasons, it seems that if there is an increase in radiation-induced thyroid carcinoma in those exposed as adults to Chernobyl fallout, it will be very much lower than the increase seen in those exposed as children.

By 2006, 20 years after the accident, the WHO and IAEA reported that over 4000 thyroid carcinomas had occurred in those under 19 at exposure in Belarus, Ukraine,
and the contaminated areas of the Russian Federation. These figures must be considered carefully. There is no doubt that ascertainment increased, because of both screening and increased awareness of the risk. This would lead to more cancers being discovered at a younger age. In addition there is no reason to suppose that the increase in incidence stopped at the borders of the countries or the designated contaminated areas. Virtually all of Europe was exposed to fallout containing isotopes of iodine, with some areas – often mountainous areas which experienced rain as the radioactive cloud passed overhead – exposed to relatively high levels, but still much less than the areas close to the reactor. There is at present no irrefutable evidence of a Chernobyl-related increase in thyroid carcinoma in areas remote from the reactor. In trying to estimate the possible risk there is a considerable debate as to whether it is appropriate to apply a linear-no-threshold (LNT) model. The LNT model is the accepted approach, and if this is applied to most of Western Europe the expected increase in thyroid carcinoma due to Chernobyl has been estimated as about 16 thousand cases, but these would be spread over a large population over many years, and the change in incidence in most areas would be too small to be detectable with standard epidemiological approaches.

Uncertainties about the dose, the population studied, the LNT model, and the DDREF (dose and dose rate effectiveness factor) all contribute to the great variation in the estimates for the total number of deaths expected to occur as a result of the Chernobyl accident. The press release from the 2006 WHO/IAEA 20 year anniversary conference gave a figure of 4000, without making it clear that this referred to the designated contaminated areas only. Greenpeace has quoted figures of over 100,000, while Cardis estimated 15,700 deaths across the whole of Europe up to 2065. Cardis also pointed out that this figure represented less than 0.01% of all cancer deaths expected in the same population over the same period. Only a small proportion of these deaths are likely to be from thyroid carcinoma. Twenty years after the accident only 15 deaths had been reported in those exposed under the age of 19 in the contaminated areas, and that figure did not separately identify patients with medullary carcinoma, which is a significant cause of death in unexposed children in that age group. Because of the slow growth of differentiated thyroid carcinoma, death from the disease may occur decades after the initial diagnosis. Further deaths will undoubtedly occur, but the survival rate is likely to be well over 90%, and probably over 95%.
PATHOLOGY AND MOLECULAR BIOLOGY

The earliest cases in the dramatic rise in incidence of thyroid carcinoma in children were all papillary carcinomas. In the first few years 98% of Belarussian and 94% of Ukrainian cases were PTCs. As the exposed population aged the proportion of follicular carcinomas has increased slightly, but there is as yet no proof that this is due to radiation, and the proportion of papillary carcinomas in those who were under 18 at exposure in Belarus has remained above 95% in most years. The incidence of thyroid carcinoma in unexposed young children is so low that virtually all the early exposed cases in young children can be assumed to be radiation induced. However as those exposed as children reach adulthood, their increased risk continues, but spontaneous tumours form an increasing proportion of the total.

While the great majority of the tumours are PTCs, there have been interesting changes in the frequency of different subtypes of PTC. The earliest reports commented that nearly all showed a solid subtype, and speculated that this could be a marker of radiation induced tumours. Later studies showed a decline with time in the proportion of the solid subtype and an increase in the proportion of the classic subtype. Quantification of the morphological changes showed that these changes were significant; the less mature solid tumours also showed more direct invasion than the more mature classic papillary carcinomas. Because the great majority of tumours occurred in children who were very young at exposure, the changes correlated both with increasing age and increasing latency. Study of a group of tumours in children who were older at exposure showed that latency was the key factor.

Molecular studies of the early Chernobyl-related tumours found that a very high proportion showed a RET rearrangement, and almost all were RET-PTC3. Again it was speculated that this rearrangement might be a marker for radiation-induced tumours. Over time, the proportion of tumours with a RET rearrangement has declined, but in the RET-positive tumours the proportion with RET-PTC1 has increased and the proportion with RET-PTC3 has decreased. TRK and RET-PTC2 rearrangements have been found in only a small proportion of tumours; various other RET-PTC rearrangements have been described, usually in single cases.

In adult non-radiated cases about half show RET-PTC rearrangements and about half BRAF point mutations, with little or no overlap. In the post-Chernobyl cases BRAF point mutations are uncommon, but the studies were carried out in young patients. In unirradiated patients BRAF mutations are less frequent in childhood than adult PTCs. It remains possible that BRAF mutations will become more common in ‘Chernobyl’ tumours as the exposed population ages, but one study of thyroid carcinomas from adults who had received external radiation found a low frequency of BRAF mutations. It is also interesting that a small number of cases with BRAF rearrangements have been found in PTCs in children exposed to Chernobyl fallout.

Several groups have investigated the relationship between morphological subtypes of PTC and the molecular pathology. All have found that the solid type of PTC is linked to RET-PTC3, and the classic type to RET-PTC1.

Two important conclusions can be drawn from these studies. The first is the importance of latency; we have seen two successive waves of tumours in those exposed to high levels of fallout as children, each with different molecular, morphological and clinical findings. It is impossible to predict with certainty what further waves of tumours may occur. A diagrammatic representation of the genotype–phenotype-latency–clinical behaviour interaction is shown in Figure 2.
These studies also allow the construction of a plausible scenario to explain the pathobiology of the development of these tumours. While most spontaneous and chemical carcinogen-induced mutations are point mutations, radiation preferentially induces double-strand DNA breaks, which can lead to deletions and rearrangements. Although a variety of rearrangements may occur, some will be lethal, and only those that lead to increased growth in the follicular cell are likely to increase the chance of carcinogenesis. RET-PTC3 has been shown in vitro to induce a higher growth rate than RET-PTC1, and it may well be that this explains the shorter latency and greater aggressiveness of RET-PTC3 tumours. The range of rearrangements induced by radiation is also likely to be influenced by the interphase arrangement of DNA; in the follicular cell nucleus the break points for RET-PTC1 have been shown to lie very close together. They lie at the crossover point where the DNA strand forms a loop, so that a single ‘hit’ could break both strands. If they are then joined wrongly, the inversion that is seen in RET-PTC1 is formed. Attempts have been made to identify a radiation-specific pattern of expression using microarrays, but there is at present no consensus.

FACTORS INFLUENCING THE RISK OF THYROID CARCINOGENESIS

The main risk factor is the radiation dose to the thyroid. The Chernobyl accident is estimated to have released about $1.7 \times 10^{18}$ Bq of iodine-131, and although large amounts of much shorter-lived isotopes of iodine as well as tellurium-132, decaying to iodine-132, were released, these are of importance only for the population living close to the reactor and exposed within a very short time of the accident. Thyroid radioactivity was directly measured in thousands of those exposed, but measurements were not made immediately after exposure, release continued for about a week, and

<table>
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<th>Mutation</th>
<th>RETPTC3</th>
<th>RETPTC1</th>
<th>? BRAF, RAS, PAX8</th>
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<td>Latency</td>
<td>4–10 years</td>
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Estimated, (start-peak)
doses have had to be reconstructed from the available data. Despite this, a strong relationship was found between the dose received in childhood and the subsequent risk of thyroid cancer, with in one study an odds ratio at 1 Gy of 5.5–8.4, depending on the model used.19 This estimate is in the same range as that for the risk of thyroid carcinogenesis following external radiation.

The risk of developing thyroid carcinoma after Chernobyl is also strongly correlated with a young age at exposure (Figure 3).9 Twelve years after the accident the number of thyroid carcinomas in Belarus in those who were under 1 at the time of the accident was 220, and the number fell rapidly with age at exposure: 22 cases occurred in those who were aged 10 at the accident.20 Some at least of the age correlation is due to the higher dose received by the thyroid of young children living in an area of fallout without taking any precautionary measures. The main route by which radioactive isotopes of iodine reach the body is through milk. Fallout on grass is ingested by cows, their mammary epithelium concentrates the iodine, and children drink relatively more milk than adults. Nursing mothers also drink a lot of milk, and the lactating human mammary epithelium also concentrates iodine. In addition, the uptake of radioactive iodine is relatively greater in the young child, dropping with age. It is likely that there is also a difference in biological susceptibility to radiation carcinogenesis in the thyroid, as an age-related risk was also found in children exposed to external radiation.

A further important susceptibility factor is the iodine status. The areas around Chernobyl are relatively iodine-deficient, and in Belarus children from areas with a stable iodine intake in the lower tertile were found to have approximately 3 times the risk of those in the upper tertile.19 Iodine deficiency affects the uptake of radioactive iodine, and therefore the dose to the gland, but most of the effect depends on the increased size of the gland that follows long-term iodine deficiency. Iodine deficiency is likely to affect the consequences of exposure of a population to iodine-131 in fallout in a number of ways. A quantitative morphological study found that there was no difference between thyroid carcinomas from children exposed to fallout after Chernobyl and age-matched children from the same areas born after the accident. There were, however, marked differences between childhood PTCs from the Chernobyl area and those from Japan, with PTCs from England and Wales being generally intermediate. The Japanese tumours showed much greater differentiation and less aggressiveness than the Chernobyl area tumours. While ethnic causes could not be

![Figure 3. Change in sensitivity to thyroid carcinogenesis after Chernobyl with age at exposure.22](image-url)
excluded, the very large differences in iodine status were thought to be the most likely cause. A molecular comparison could not be carried out, so it was not possible to determine whether the less rapidly growing thyroids in Japan were less susceptible to the RET-PTC3 rearrangement, or the effect of the rearrangement was modified by the lesser growth stimulation resulting from high levels of dietary iodine. Iodine deficiency is a possible factor in the unexpectedly short latent period for the first increase in thyroid cancers after Chernobyl, only 4 years after the accident.

Another potentially important factor influencing the risk of developing thyroid cancer after Chernobyl is genetically determined susceptibility. Non-medullary thyroid cancer has a relatively high familial element in non-radiated cases, but while genes have been identified that are associated with familial follicular and oxyphil tumours, and with the special type of thyroid cancer associated with familial adenomatous polyposis, no gene has yet been linked with ‘ordinary’ papillary carcinomas. PTCs were found in exposed siblings after Chernobyl more often than would have been expected by chance, but as yet no specific genetic link has been demonstrated. Some genes are known to be associated with the repair of DNA double-strand breaks, among them the BRACA genes. In view of the link between thyroid and breast cancer the possibility of germline defects in BRACA as well as other dsb repair genes needs investigation.

CLINICAL OUTCOME OF THYROID CARCINOMAS

Despite the large numbers of thyroid carcinomas that have occurred in those who were exposed to high levels of fallout from Chernobyl as children, the number of deaths from thyroid carcinoma has been very low; 15 deaths were reported by the WHO/IAEA 20-year review, but deaths from causes other than thyroid disease were not separately identified, nor were deaths from medullary carcinoma. The aggressiveness of the early cases has been well documented, and in these cases direct extrathyroid invasion and lung metastases were relatively frequent. The results of surgical treatment of 740 cases of childhood thyroid cancer from Belarus have been reported in a recent important paper; 92% had been exposed to Chernobyl fallout, 95% were PTCs, and nine of these had a family history of thyroid malignancy. Lymph-node spread was found in 69% of cases, lung metastasis by conventional x-ray in 2.3% (17 cases), but the first post-therapeutic radiiodine scan showed lung spread in 76 cases. Lung metastasis was strongly associated with a young age at presentation. Total thyroidectomy was recommended for childhood thyroid carcinoma, and was carried out in the majority of patients. Radioiodine therapy was used for ablation of thyroid remnants and/or lung metastases in 63% of cases. The outcome was excellent, with 5- and 10-year survival for the whole series of 99.5 and 98.8 respectively. Of the eight patients who died, three died of causes other than thyroid cancer, three from medullary carcinoma, and one from follicular carcinoma. Only one person died from papillary carcinoma; this patient, with widespread pulmonary metastases, was one of the early cases, and was not treated with radiiodine. These results underline the generally good prognosis of appropriately treated childhood papillary carcinoma, but of the 128 patients with lung metastases complete remission was achieved in 37 of 128 cases, and those with incomplete remission are still maintained on radioiodine therapy.

There is of course a risk of complications from treatment. In the series just discussed, 6.2% suffered permanent recurrent laryngeal nerve damage, and 12.3% permanent hypoparathyroidism. These figures are higher than in adult series, but at least
in part reflect the difficulty of surgery in small children often with local tumour spread. Second malignancies have been reported after radioiodine therapy in adults, and one report refers to the occurrence of one salivary gland tumour and one syringoepithe- lioma in a follow-up of 245 radioiodine-treated thyroid carcinomas from Belarus. Salivary-gland tumours are known to be radiation-induced, and an increased risk of their occurrence has been reported after radioiodine therapy. It is important to balance the risks and benefits of high-dose radioiodine therapy for children with thyroid carci- noma, and the risks include pulmonary fibrosis as well as second malignancies. Studies of the very large cohort of childhood thyroid carcinomas after Chernobyl should pro- vide very valuable information to help in these decisions.

With increasing latency the patient are of course older, and the tumours have in general become less aggressive. It currently seems likely that the eventual cause- specific death rate for the tumours that have occurred in the first 20 years after the accident will be less than 5%, possibly much less. Hopefully this trend will continue for cases that will arise in the future, but it remains possible that different mutations may lead to tumours with a different morphology and different clinical behaviour.

OTHER THYROID EFFECTS

An increase in thyroid nodularity in more exposed areas was an early finding, although interpretation was complicated by the variable levels of iodine deficiency. A Ukrainian study has shown an increase in the incidence of follicular adenomas in exposed chil- dren and adolescents, with a linear dose–response relationship. The risk was smaller than the risk for carcinoma, but it must be remembered that the mean latency for fol- licular adenomas after external radiation was longer than that for carcinomas, so the risk ratios may change with time.

Autoimmune thyroid disease has been linked to radiation; it also occurs in associ- ation with PTC. In a large cohort study, no radiation-related increase in autoimmune thyroiditis was found. However, there was a modest link between radiation dose and the levels of thyroid peroxidase antibodies, which was present in cancer-free individuals.

NON-THYROID DISEASES

Because of the early and dramatic increase in thyroid carcinoma incidence, most of the attention on the health consequences of the Chernobyl accident has been focused on the thyroid. The psychosocial consequences have been briefly discussed, and are im- portant. The nature of the radiation exposure suggests that non-thyroid consequences could follow exposure to isotopes of iodine or to other isotopes, including strontium which is bone-seeking and caesium which is generally distributed throughout the body. Cs-137 with a half life of 30 years is still present at above generally accepted safe levels in areas surrounding the exclusion zone. The very high dose to the thyroid from io- dine-131 is dependent upon the ability of the gland to concentrate, bind and store the isotope. A variety of epithelia possess the iodide symporter, allowing them to con- centrate iodide, but the absence of binding and storage means that the tissue dose is very much less than that of the thyroid. Mammary epithelium, particularly during lac- tation, concentrates iodine-131, and an increase of breast cancer in young women in Gomel Oblast has been reported. It is not clear yet whether the increase is related to lactation at the time of Chernobyl. The most susceptible time for radiation-induced
breast cancer in the atomic bomb studies was at puberty, but it is uncertain whether pubertal breast epithelium has a functional iodide transporter. Exposure to iodine-131 does involve an element of whole-body radiation, as does exposure to other radioactive isotopes, especially caesium. The possibility that breast cancer may occur in the future in post-Chernobyl thyroid cancer patients who were treated at a young age with high doses of radioiodine also needs consideration.

A well-documented radiation-induced malignancy is leukaemia, and radiation from isotopes of strontium bound to bone could have contributed to the marrow dose. Increases in leukaemia incidence in exposed populations have been both claimed and denied; a recent assessment concludes that, apart from clean-up workers, there is no proof of a link to exposure. There have been reports, sometimes anecdotal, of increases in a variety of other tumours in those exposed to Chernobyl fallout, including for example brain and kidney. In the absence of thorough epidemiological studies, based on verified diagnoses and taking into account the problems of ascertainment, it is difficult to be certain that these are Chernobyl-related increases. What they do show is the continuing need for well-supported long-term studies similar to those still being carried out after the atomic bombs.

GERMLINE EFFECTS

The possibility that radiation can lead to germ-cell mutations that can be transmitted to subsequent generations has been known for many years, but has been associated with relatively high doses of radiation. The finding of minisatellite instability in the unexposed children of fathers exposed to Chernobyl fallout was unexpected and concerning. The technique is very sensitive, and there is as yet no evidence of any physical disease in those carrying the instability. The dose to the testis from fallout would be orders of magnitude lower than the thyroid dose, unless there was an unexpected concentration in the testis of one of the radioactive isotopes released. Several authors have failed to find significant elevation of mini- or micro-satellite mutations in children of Chernobyl clean-up workers.

CONCLUSIONS

The accident at Chernobyl in 1986 led to the world’s largest release of radioactivity, and to the largest number of tumours of one type due to one cause on one date that has ever occurred. While it is true to say that the overall effects have been less disastrous than many feared, and that the projected Europe-wide health effects pale into insignificance besides those of tobacco, the effect of the accident on the lives of hundreds of thousands of people living around the reactor have been catastrophic.

The health consequences of radiation exposure after Chernobyl differ greatly from those after the atomic bombs. The major consequences that have followed from exposure to fallout have been discussed, and reviewing the situation after over 20 years a number of principles emerge. Radiation induces a range of mutations; those that confer a growth advantage or an increased liability to further mutations will be selected. Different mutations or mutational pathways will lead to tumours with different molecular, morphological and clinical characteristics, and especially with differing latent periods. It follows that observations at any one period must be interpreted with care: a good example was the belief that radiation-induced thyroid tumours were more aggressive than sporadic tumours, and that solid PTCs and RET-PTC3 rearrangements...
were typical of radiation-induced thyroid tumours. We now recognize that these were all features of short-latency tumours, and the findings changed with increasing latency. The search for a radiation-specific molecular marker has not produced results; it may be that the main molecular characteristic of radiation-induced tumours is a high frequency of rearrangements or deletions compared to point mutations. Another lesson comes from the attitude in the West to the early reports of an increased incidence in childhood thyroid carcinomas only 4 years after the accident. The scepticism was based on the dogma that the latent period for radiation-induced thyroid carcinoma was 10 years, and that iodine-131 carried low or no carcinogenic hazard. Both dogmas were wrong. The first was based on external radiation in an iodine-sufficient population with very many fewer children studied than were exposed after Chernobyl; the second was based on experiences with iodine-131 administered to adults, mostly using high doses as therapy. In retrospect, it was not appropriate to apply this experience to the exposure of millions of children living in iodine-deficient areas to sub-ablative doses of iodine-131.

The final point arises from a comparison with the experience after the atomic bombs. Comprehensive international studies were set up to monitor the long-term health consequences. The great majority of these effects did not become apparent until more than 20 years after exposure. It may well be that because of the different pattern of radiation exposure the same will not be true after Chernobyl. However, if the international community does not support studies of the effects both in the high-exposure areas around the reactor and in more distant low-dose areas for the life-time of those exposed, the full consequences of exposure to fallout may never be known.

**SUMMARY**

Studies of the consequences of the massive release of radioisotopes in the first 2 decades after Chernobyl have increased our understanding of radiation and thyroid carcinogenesis. While radiation from iodine-131 has little or no carcinogenic risk to adults, children are at particular risk, and the risk is greatest for infants. This has considerable significance for protection in the event of a similar accident. The latent period may be no more than 3–4 years, and those exposed in childhood carry the risk with them into adulthood, certainly for 20 years; without life-time studies the full risk cannot be assessed. The nature of the exposure to iodine-131 with its short half-life, the huge size of the exposed population, and the large number of thyroid carcinomas that have occurred allow a correlation with latency. To date virtually all the tumours are PTCs, and latency correlates with different RET-PTC variants, morphology and clinical behaviour. Tumours with longer latency, yet to occur, may show other different patterns. Despite the initial conclusions that radiation-induced tumours were unusually aggressive, it is now evident that the aggressiveness is linked to short latency rather than radiation, and the overall death rate to date is extremely low; only one Belarussian patient from over 600 Chernobyl-related PTCs has so far died from the disease. There are many unanswered questions: the degree to which screening has contributed to the size of the outbreak, the need for aggressive treatment has been shown for young patients, but will it be needed for small tumours as those at risk age and are subject to intensive screening? The risks of radiation therapy for young patients who have already been exposed to radiation need to be evaluated. Above all, diagnostic, molecular morphological and clinical studies need to be continued for the life-time of those at risk.
REFERENCES


